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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/648,692	08/25/2000	J. Oliver Dolly	17311(AP)	6378

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EXAMINER	
BUGAISKY, GABRIELE E	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/648,692	DOLLY ET AL.	
	Examiner	Art Unit	
	Gabriele E. BUGAISKY	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/19/2004; 7/23/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-33 and 35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-33 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment of 4/19/2004 is acknowledged. Claims 1-19 have been canceled. Claims currently pending are 20-33 and 35-37.

Information Disclosure Statement

A copy of the Borodic et al. (AX) reference was received 19 April 2004. It has been initialed as considered on a copy of the PTO-1449 submitted 19 April 2001.

Oath/Declaration

The oath or declaration remains defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Arguments submitted 19 April 2004 are noted. The Examiner believes that Applicants have misinterpreted 37 C.F.R. § 1.52(c), which should be read as: "Any. . . alteration. . . should be 1) dated AND 2) intitialed or signed by the applicant. . ." The rule is intended to protect Applicants.

Specification

The abstract of the disclosure remains objected to because the first sentence contains no verb. Correction is required. See MPEP § 608.01(b). Applicants state in their response:

'The first sentence of the abstract is as follows "Compositions comprising activatable recombinant neurotoxins and polypeptides derived therefrom." The Applicants respectfully submit that the first sentence of the abstract does contains a verb, namely "comprising." Therefore, the Applicants respectfully request the withdrawal of the objection.'

Applicants are incorrect in their assertion. As used, "comprising" is a preposition, and not a verb. "Comprise" or "comprises" is a verb.

The objection to the disclosure is withdrawn, based upon the amendments.

The application now appears to be in compliance with 37 C.F.R. 1.821-1.825.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 33 remains rejected and claim 32 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 recites the limitation "derived from a clostridial neurotoxin comprising a) inserting the plasmid of any of claims 20-25 or 29-31. . ."

. There is insufficient antecedent basis for this limitation (clostridial neurotoxin) in claims 20-22 and 29-31 .

Claim 33 recites the limitation "derived from a clostridial neurotoxin comprising". . . "the plasmid of either of claims 21 or 22. . ."

There is insufficient antecedent basis for this limitation (clostridial neurotoxin) in claims 21 or 22.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 20, 23-29 and 32 remain rejected and claims 35-37 are newly rejected under 35 U.S.C. 102(b) as being anticipated by WO98 /07864 (Shone *et al.*) , for reasons of record. The reference provides for recombinant plasmids comprising single chain peptides from clostridial neurotoxins: The abstract states e.g.,

" The polypeptide thus combines useful properties of a clostridial toxin, such as a botulinum or tetanus toxin, without the toxicity associated with the natural molecule. The polypeptide can also contain a third domain that targets it to a specific cell, rendering the polypeptide useful in inhibition of exocytosis in target cells."

Applicant's arguments filed 19 April 2004 have been fully considered but they are not persuasive. The discussion is directed towards the rejections of the original claims. It is stated that "the resulting construct still does not contain a binding element, such as one present in the Hc portion of BONT/A, and the construct contatiniing a protease cleavage site is cleaved by a human protease (Factor Xa)." Please note that the amended claim 20 recites that the 3rd sequence region comprises a therapeutic element having biological activity and that it not be cleaved by a human protease. The 4th region is the protease cleavage site; as a note in point, the limitation is meaningless as there is no protease cleavage site that is not cleaved by at least one human protease.

Applicants are incorrect that no binding element is provided. Shone *et al.* provide $L_{FXa}/3$ H_{423} /A-IGF-1 (SEQ ID NO: 14), in which the carboxy-terminal domain has a sequence equivalent to that of insulin-like growth factor-1 (IGF-1) and is able to bind to the insulin-like growth factor receptor with high affinity. (LH_{423} /A fragment is a polypeptide of 871 amino acid residues corresponding to the entire light-chain (LC, 448 amino acids) and 423 residues of the amino terminus of the heavy-chain (Hc) of botulinum neurotoxin type A. The variant $L_{FXa}/3$ H_{423} /A contains a specific proteolytic cleavage site incorporated at the carboxy-terminal end of the light chain domain, specifically after residue 448 of LH_{423} /A.)Thus, the plasmid construct contains the following : a) a clostridial heavy chain domain attached to a IGF sequence that

specifically binds to cells expressing insulin-like growth factor receptor b) a clostridial light chain which is not cleaved by human factor Xa, and c) a factor Xa protease cleavage site.

Claims 20, 23-29 and 32 remain rejected and claims 35-37 are newly rejected under 35 U.S.C. 102(e) as being anticipated by Shone *et al.*(US patent 6461617.) , for reasons of record. Applicants are correct that the disclosure of this reference is identical to the above WO patent; however, this rejection is proper as it is applies a different section of 35 U.S.C. 102. The above discussion is incorporated here.

The rejection of claims 21-22 and 33 under 35 U.S.C. 102(b) as being anticipated by WO98 /07864 (Shone *et al.*) is withdrawn,

The rejection of claims 21-22 and 33 under 35 U.S.C. 102(e) as being anticipated by US patent 6461617. (Shone *et al.*) is withdrawn,

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-29, 31-33 remain rejected and new claims 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shone *et al.* (US patent 6461614), for reasons of record. Further, in column 5, lines 23-37, it provides for fusion proteins incorporating a polypeptide (such as a GST-tag) for binding to a column for affinity purification. It would have been obvious for one of ordinary skill in the art at the time of the invention to modify the plasmid encoding $L._{FXa}/3\ H._{423}$ /A-IGF-1 with an additional affinity purification tag, with a reasonable expectation of success. With respect to binding to specific cell types recited in claim 30, Shone et al. discuss that any type of bonding domain could be incorporated into the construct. Thus one of ordinary skill in the art at the time of the invention would have expected to substitute any specific ligand binding domain known to be expressed in specific cells for the IGF-1 of the plasmid encoding $L._{FXa}/3\ H._{423}$ /A-IGF-1, with a reasonable expectation of success.

Applicant's arguments filed 19 April 2004 have been fully considered but they are not persuasive. Applicants arguments rest on assertion that as the reference is not anticipatory for claim 20, it cannot render obvious the instant claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gabriele E. BUGAISKY whose telephone number is (571) 272-0945. The examiner can normally be reached on Tues.- Fri 8:15 AM-1:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8800.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gabriele E. BUGAISKY
Primary Examiner
Art Unit 1653